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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/693,233	10/24/2003	Zehra Kaymakcalan	BBI-190RCE	1420

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EXAMINER	
SKELDING, ZACHARY S	
ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/693,233	KAYMAKCALAN ET AL.	
	Examiner	Art Unit	
	ZACHARY SKELDING	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-17,21,22,24,31,34,35,42,43,45,48 and 52-55* is/are pending in the application.

4a) Of the above claim(s) *52 and 53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-17,21,22,24,31,34,35,42,43,45,48,54 and 55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's amendment and remarks filed December 10, 2008 has been entered.

   Claims 1-14, 18-20, 23, 25-30, 32-33, 36-41, 44, 46-47, 49-51 and 56 have been canceled.

   Claims 15, 21, 24, 42, 48, and 52-55 have been amended.

   Claims 34 and 35 are explicitly recited in the current claim set and yet the claims also indicate 34 and 35 are canceled. Applicant is requested to clarify for the record if claims 34 and 35 are pending or canceled. For the purposes of this action it will be assumed that claims 34 and 35 are pending.

   Claim 31 has the claim status identifiers "currently amended" and yet no underscore or strikethrough is evident. Applicant is requested to clarify for the record if claims 31 has been amended and to show the appropriate underscore or strikethrough if so.

   Thus, claims 15-17, 21, 22, 24, 31, 34, 35, 42, 43, 45, 48, and 52-55 are pending.

   Moreover, 15-17, 21, 22, 24, 31, 34, 35, 42, 43, 45, 48, 54 and 55 are under examination as they read on a method for treating arthritis comprising administering by injection to a subject a fully human anti-TNFα antibody, or an antigen-binding portion thereof, in a low dose of 0.01 - 0.1 mg/kg at a frequency of not more than once per week, such that the arthritis is treated as demonstrable by a variety of measures, wherein the anti-TNFα antibody has certain physical properties, or methods of treating arthritis with infliximab at a dose of 0.5 – 1.0 mg/kg at a frequency of not more than once per week, such that the arthritis is treated as demonstrable by a variety of measures.

   Claims 52 and 53 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on November 12, 2004.

2. This Office Action is in response to applicant's amendment and remarks filed December 10, 2008.

   The previous rejections of record can be found in the Office Action mailed September 10, 2008.

The previous rejection under 35 U.S.C. § 102(a) has been withdrawn in view of applicant's amendment to the claims.

The previous rejection under 35 USC 112, 1st paragraph, written description has been withdrawn in view of applicant's amendment to the claims.

The previous rejection under 35 USC 112, 1st paragraph, enablement has been withdrawn upon further consideration.

New Grounds of Rejection are put forth below.

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 15-17, 21, 22, 24, 31, 34, 35, 42, 43, 45 and 48 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Stephens et al. (Antibody Therapeutics (1997), pp 317-340, eds. Harris et al., CRC: Boca Raton, Fla.), in view of Salfeld et al. (US Patent No. 6,258,562), den Broeder et al. (Rheumatology (Oxford). 2002 Jun;41(6):638-42) and in response to applicant's argument further in view of Joachim Kempeni (Ann Rheum Dis. 1999 Nov;58 Suppl 1:I70-2), cited on an IDS.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Applicant argues the instant claims are non-obvious over the cited references because the references allegedly fall short in their teachings as combined, teach away from the claimed invention, and motivation to combine the cited references is lacking.

Applicant's arguments have been considered, but have not been found convincing, essentially for the reasons of record as put forth in the Office Action mailed August 8, 2008 and March 4, 2008.

The Stephens Reference

1) Applicant argues "a skilled artisan would not rely on the teachings of Stephens for any motivation or suggestions regarding dosage or other characteristic of a fully human antibody" because Stephens teaches the use of a humanized anti-TNFα antibody not a fully human anti-TNFα antibody, and "dosages of a humanized antibody and of a fully human antibody would not be expected to correlate".

2) Applicant further argues "One of ordinary skill in the art would not have been motivated, based on the disclosure of Stephens, to treat arthritis with a low dose of 0.01-0.1 mg/kg, since Stephens provides no evidence that a 0.1 mg/kg dose of CDP571 is effective in treating arthritis and, moreover, teaches that a low dose of an antibody mounts an immune response and is cleared from the patient's system to a greater extent than a higher dose, e.g., 10 mg/kg, of CDP571. Applicants therefore urge that Stephens teaches away from the claims as amended."

(see Applicant's remarks filed December 10, 2008, page 7, 2nd paragraph, applicant's emphasis shown).

Considering applicant's second argument first, as stated in the prior Office Action, Stephens teaches a method of treating rheumatoid arthritis comprising administering a single 0.1 mg/kg dose of humanized anti-TNFα antibody, CDP571. Stephens further teaches that the disease activity measures included tender and swollen joints, and that patients who received placebo did not improve whereas CDP571 had a dose-dependent effect on all patients treated (see entire document, in particular pages 326-327). Furthermore, all patients receiving CDP571 scored a reduction in pain scale by week 1 as taught by the following: "First infusion - *Patients who received placebo did not improve. In contrast, there was a dose-dependent effect of CDP571 treatment* with maximum patient responses after 10 mg/kg...*All patients who received CDP571 scored a reduction in pain scale by week 1.*" See, Stephens, page 327, 1st paragraph, emphasis added.

Thus, in contrast to applicant's argument, the examiner's position continues to be that Stephens ***does*** teach the treatment of arthritis with a single dose of 0.1 mg/kg humanized anti-TNFα antibody.

Furthermore, with respect to applicant's argument that Stephens *teaches away* form the claimed invention, while Stephens does teach increased CPD571 clearance when patients are treated over particular time periods and at particular dosages, i.e., 8 weeks after a single administration of 0.1 mg/kg CDP571 anti-TNFα there is an increase in anti-CDP571 IgG production, and subsequent doses of CDP571 anti-TNFα antibody at 1 or 10 mg/kg resulted in increased CPD571 clearance, this does not negate the other teachings of Stephens that, in contrast to the placebo treatment, treatment with CDP571 anti-TNFα antibody had a dose-dependent effect on the treated patients, and ***all*** patients receiving anti-TNFα antibody scored a reduction in pain scale by week 1.

Thus, while Stephens teaches that under certain limited conditions (which fall within the scope of the instant claims but certainly do not fully encompass the scope of the instantly claimed method) the effectiveness of CDP571 anti-TNFα antibody would expected to be compromised, Stephen's nevertheless teaches that treatment of rheumatoid arthritis with 0.1 mg/kg CDP571 anti-TNFα antibody is effective.

Furthermore, the teachings of Salfeld provide a solution to the issue of CDP571 clearance that would be readily recognized by one of ordinary skill in the art.

In particular, one of ordinary skill in the art would have been motivated to substitute the human D2E7 antibody of Salfeld for the humanized CDP571 antibody of Stephens because, as taught by Salfeld, a fully human antibody, such as D2E7, is preferable to a humanized antibody, such as CDP571, which is 95% human/5% murine, because even a small amount of non-human sequence can elicit an unwanted immune reaction, especially so when administered over long periods of time as in the treatment of chronic rheumatoid arthritis (see Salfeld, paragraph bridging columns 1-2).

With respect to applicant's first argument about the Stephens reference, the examiner disagrees that one of ordinary skill in the art would not "rely on the teachings of Stephens for any motivation or suggestions regarding dosage or other characteristic of a fully human antibody" because Stephens teaches the use of a humanized rather than a fully human anti-TNFα antibody to treat rheumatoid arthritis.

If anything, the skilled artisan would reasonably expect substitution of a fully human anti-TNFα antibody, such as the D2E7 antibody taught by Salfeld, to be effective at lower doses than the humanized anti-TNFα antibody CDP571 given the reduced immunogenicity of a fully human antibody which results in a longer serum half-life, see e.g., Joachim Kempeni, teaching that D2E7 has a mean serum half-life of around 11.6 to 13.7 days in rheumatoid arthritis patients whereas as shown by Stephens, the half-life of CDP571 is far less than 10 days at doses encompassed in the instant claims, for example, the CDP571 half-life is 5 days when administered at 0.1 mg/kg. (See Stephens page 321).

The Salfeld Reference

1) Applicant acknowledges Salfeld "provides general guidance with regard to normally prescribed dosing" of anti-TNFα antibody at 0.1–20 mg/kg. However, applicant argues Salfeld fails to provide a reasonable expectation of success for treating arthritis at the claimed doses. In this regard applicant argues (applicant's emphasis) "…Salfeld disclosed only treatment of rheumatoid arthritis using a range of 1.5 mg/kg to 30 mg/kg (see Example 4, part D, section III, Table 15). Salfeld thus fails to teach or suggest the treatment of arthritis in the 0.01-0.1 mg/kg range."

2) Moreover, applicant argues that, given the teachings of Salfeld that 0.1-20 mg/kg is an effective dose of anti-TNFα antibody, one of ordinary skill in the art would not have been motivated to use a dose of 0.01-0.1 mg/kg anti-TNFα antibody to treat rheumatoid arthritis. Applicant continues, "[f]urther, when considering prior art disclosing a range which "touches" the claimed range, 'unexpected results [within the claimed narrow range] may.., render the claims unobvious' (see M.P.E.P. §2131.03). In the present case, while the Salfeld discloses a dose range which 'touches' the claimed dose range of 0.01-0.1 mg/kg, the unexpected results provided by Applicants further prove that the pending claims are unobvious over the teachings of Salfeld."

As to applicant's first argument, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

If the Salfeld reference disclosed treatment of arthritis with "sufficient specificity to constitute an anticipation under the statute" it would be grounds for an anticipation rejection. However, it is instead part of this obviousness rejection because 0.1 mg/kg is a dose contemplated by Salfeld for the treatment of arthritis with a fully human anti-TNFα antibody, and when considered along with the teachings of the other references cited in this rejection, it would have been obvious to one of ordinary skill in the art, and one of ordinary skill in the art would have been motivated to use 0.1 mg/kg of fully human anti-TNFα antibody at a frequency of not more than once per week to treat arthritis.

As to applicant's second argument, applicant's "unexpected result" is that mice transgenic for TNFα (tg197 mice), which is one model system for rheumatoid arthritis, can allegedly have their arthritis symptoms alleviated with 0.01 – 0.1 mg/kg anti-TNFα antibody. Therefore, applicant alleges human rheumatoid arthritis could also be treated with the same dose.

However, applicant has not established the closest prior art and compared it to their results to establish why their results were unexpected.

"A comparison of the *claimed* invention with the disclosure of each cited reference to determine the number of claim limitations in common with each reference, bearing in mind the relative importance of particular limitations, will usually yield the closest single prior art reference." *In re Merchant*, 575 F.2d 865, 868, 197 USPQ 785, 787 (CCPA 1978) (emphasis in original). See MPEP § 716.02(e).

Nevertheless, assuming that den Broeder is the closest prior art, den Broeder teaches a dose titration clinical trial of the D2E7 anti-TNFα antibody in which rheumatoid arthritis patients were effectively treated with a dose of 0.25 mg/kg/2-4 weeks.

While den Broeder teaches their trial was not designed to include D2E7 anti-TNFα antibody dose steps smaller than 0.25 mg/kg, den Broeder further teaches that the D2E7 anti-TNFα antibody dosage could be even further reduced in light of the absence of any disease flare-ups in the patients treated with 0.25 mg/kg D2E7 every 2-4 weeks. Furthermore, den Broeder teaches that even lower dosages are "supported by the remarkably long duration of response seen in some patients after only one administration of anti-TNF-α antibody, documented for both D2E7 (up to 14 weeks EULAR response) and infliximab (up to approximately 18 weeks Paulus 20 response)." (see den Broeder, in particular Patients and Methods, Results and Discussion, pages 639-641, including 641 2nd paragraph).

Converting the 0.25 mg/kg/2-4 weeks dosage of den Broeder to a per week basis gives 0.0625 – 0.125 mg/kg/week, which overlaps the claimed dosage range of 0.01 to 0.1 mg/kg.

Indeed, treatment of arthritis patients via the claimed methods was obvious when the teachings of Stephens, Salfeld and den Broeder are considered in combination through the lens of one of ordinary skill in the art .

The den Broeder reference

1) Applicant argues "Den Broeder discloses a much larger dose of 2.5 mg/kg delivered intravenously every 2-4 weeks. At no time does Den Broeder inject less than a 0.25 mg/kg dose, which is well above and outside Applicants' dose range required in the claims as amended. Den Broeder reports that 'six out of 21 patients were placed back on the original dose of 3.0 mg/kg after flaring on 1.0 mg/kg, whereas nine, three and three patients respectively reached a dose of 1.0, 0.5 and 0.25 mg/kg.' Further, den Broeder discloses that, based on these results, the median of the calculated weekly dose of anti-TNFα administered to these patients was 0.36 mg/kg per week. Thus, den Broeder fails to teach or suggest a method of treating arthritis by administering a dose lower than 0.25 mg/kg, let alone a low dose of 0.01-0.1 mg/kg of an anti-TNFα antibody, as required by the instant claims." (page 8, 2nd paragraph to page 9, 1st paragraph, applicant's emphasis shown)

2) Applicant further argues (applicant's emphasis), "One of skill in the art would not have been motivated, based on the disclosure of den Broeder, to practice the claimed invention of treating arthritis at a low dose of 0.01-0.1 mg/kg because Den Broeder teaches away. Den Broeder teaches that '[a] drawback of step-down dose titration is the inevitable disease flare in the titration phase' and note that 'eighteen out of 21 patients experienced a flair of the disease' (page 641, last paragraph; emphasis added). Indeed, only three out of 21 patients reached the dose of 0.25 mg/kg, while the remaining 18 patients experienced a flair in disease at even higher doses. Thus, den Broeder teaches away from the claimed low dose of 0.01-0.1 mg/kg in that it teaches that even at a dose of 0.25 mg/kg (or greater), 18 out of the 21 patients treated experienced a flair in disease. One of ordinary skill in the art would not have been motivated nor have had a reasonable expectation of success, based on the disclosure of den Broeder, to treat with doses lower than 0.25 mg/kg, since only a small

percentage of patients (i.e., 3 out of 21) were observed to reach the dose of 0.25 mg/kg before exhibiting a flare in disease."

As to applicant's first argument, while it is true Den Broeder does not teach a dose of less than 0.25 mg/kg/2-4 weeks and further teaches that the median of the calculated weekly dose of the fully human anti-TNFα antibody D2E7 was 0.36 mg/kg/week, it is also true that for the 3 of 21 rheumatoid arthritis patients their dose could be successfully titrated down to 0.25 mg/kg/2-4 weeks which amounts to 0.0625 – 0.125 mg/kg on a per week basis. Thus one of ordinary skill in the art would have had a reasonable expectation of success in treating the symptoms of disease with 0.0625 – 0.125 mg/kg/week dose for some rheumatoid arthritis patients. This notion is consistent with the teachings of Den Broeder that "as no smaller dose steps than 0.25 mg/kg were included, one could speculate that even further reduction is possible for individual patients. This is supported by the remarkably long duration of response seen in some patients after only one administration of anti-TNFα, document for…D2E7 (up to 14 weeks EULAR response)..." (see page 641, left column, 2nd paragraph).

As to applicant's second argument, if the possibility of "disease flare" were such as strong demotivating force then why would den Broeder or any other medical practitioner of ordinary skill in the art ever undertake a "step-down dose titration" study which entails the "inevitable disease flare"? The examiner submits that one of ordinary skill in the art was motivated to do so essentially for the reasons of record put forth in the Office Action of August 8, 2008, namely that given the teaching of den Broeder, one of ordinary skill in the art would have been motivated to treat rheumatoid arthritis with the lowest possible effective dose of anti-TNFα antibody in order to minimize the risk associated with TNFα suppression, e.g., lymphoma risk, and to further minimize treatment costs (which is also emphasized by den Broeder, see Introduction at page 638-639).

It is noted that the teachings of den Broeder regarding anti-TNFα antibody dose titration are also consistent with the teachings of Salfeld that anti-TNFα antibody dosage concentration and frequency is a results effective variable that should be "adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions".

Indeed, applicant's assertion at page 8, 1st paragraph of their remarks filed November 8, 2007 that "[e]ven if, *arguendo,* some testing would be required to determine if the dose is affective on a particular patient, such experimentation would certainly not be 'undue' for a skilled artisan, since drug dosages have to be optimized for each patient regardless," is consistent with the idea that either 1. treatment naïve arthritis patient will have to continue to suffer the symptoms of disease while their lowest effective anti-TNFα dose is determined by routine optimization or 2. an arthritis patient currently being treated with anti-TNFα antibody will have to risk a disease flare in order to determine their lowest effective dose by routine optimization.

In conclusion, given the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Accordingly, the instant claims are unpatentable over Stephens in view of Salfeld and den Broeder.

It is noted that the functional properties of the anti-TNFα antibody (e.g. as recited in claim 15) are physical properties of the D2E7 antibody taught by Salfeld et al. It is further noted that treatment of specific symptoms of rheumatoid arthritis (e.g. as recited in claim 21) would necessarily be treated when treating rheumatoid arthritis with 0.1 mg/kg D2E7 at a frequency of not more than once per week, as demonstrated by the instant specification at page 29, Table 2.

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

   A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

   Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 15-17, 21, 22, 24, 31, 34, 35, 42, 43, 45 and 48 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1–7, 17, 19, 20, 36-39, 49, 51, 52, 68, 69 and 70 of U.S. Patent No. 6,509,015 in view of Stephens et al. (Antibody Therapeutics (1997), pp 317-340, eds. Harris et al., CRC: Boca Raton, Fla.),

Salfeld et al. (US Patent No. 6,258,562), den Broeder et al. (Rheumatology (Oxford). 2002 Jun;41(6):638-42) and Joachim Kempeni (Ann Rheum Dis. 1999 Nov;58 Suppl 1:I70-2).

Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons:

As a preliminary matter, it is noted that the elected species of disease under examination is "rheumatoid arthritis"; however, certain claims of U.S. Patent No. 6,509,015 reading on other species of arthritic diseases are also included in this rejection because they anticipate the instant claims drawn to the a method of treating the genus of arthritic diseases.

The reference claims are directed to a method of treating various forms of arthritis by administering an anti-TNFα antibody, alone or in combination with additional therapeutic agents. US Patent No. 6,509,015 clarifies, e.g. in columns 2-3 bridging paragraph, that the claimed methods employ antibody D2E7, i.e. the same antibody as recited in the instant claims.

Since treatment of the same disorder is claimed in U.S. Patent Nos. 6,509,015 and as in the instant application, i.e., rheumatoid arthritis, the symptoms of the disorder are inherently the same, and therefore are not patentably distinct from the instant claimed invention.

The instant claims differ from the reference teachings in the recitation of a "dose of 0.01 – 0.1 mg/kg."

However, as put forth in detail in Section 4 above, the reference claims, in view of the teachings of Stephens, Salfeld, den Broeder and Joachim Kempeni, render the claimed invention obvious.

Applicant argues the instant claims are non-obvious over the reference claims and cited references for the same reasons put forth by applicant in Section 4 above.

Applicant's argument are not found convincing for the reasons put forth in Section 4 above.

Thus, the reference claims, in view of the teachings of Stephens, Salfeld, den Broeder and Joachim Kempeni, render the claimed invention obvious.

7. Claims 15-17, 21, 22, 24, 31, 34, 35, 42, 43, 45 and 48 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 7,223,394 in view of Stephens et al. (Antibody Therapeutics (1997), pp 317-340, eds. Harris et al., CRC: Boca Raton, Fla.), Salfeld et al. (US Patent No. 6,258,562), den Broeder et al. (Rheumatology (Oxford). 2002 Jun;41(6):638-42) and Joachim Kempeni (Ann Rheum Dis. 1999 Nov;58 Suppl 1:I70-2).

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The reference claims are directed to a method of treating various forms of arthritis by administering an anti-TNFα antibody, alone or in combination with additional therapeutic agents. US Patent No. 7,223,394 clarifies, e.g. in columns 2-3 bridging paragraph, that the claimed methods employ antibody D2E7, i.e. the same antibody as recited in the instant claims.

Since treatment of the same disorder is claimed in U.S. Patent Nos. 7,223,394 and as in the instant application, i.e., rheumatoid arthritis, the symptoms of the disorder are inherently the same, and therefore are not patentably distinct from the instant claimed invention.

The instant claims differ from the reference teachings in the recitation of a "dose of 0.01 – 0.1 mg/kg."

However, as put forth in detail in Section 4 above, the reference claims, in view of the teachings of Stephens, Salfeld, den Broeder and Joachim Kempeni, render the claimed invention obvious.

Applicant argues the instant claims are non-obvious over the reference claims and cited references for the same reasons put forth by applicant in Section 4 above.

Applicant's argument are not found convincing for the reasons put forth in Section 4 above.

Thus, the reference claims, in view of the teachings of Stephens, Salfeld, den Broeder and Joachim Kempeni, render the claimed invention obvious.

8. Claims 15-17, 21, 22, 24, 31, 34, 35, 42, 43, 45 and 48 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 17, 41, 79, 86, 103, 110, 115, 122, 127 and 134 of USSN 11/233,252 (U.S. 20060024293), in view of Stephens et al. (Antibody Therapeutics (1997), pp 317-340, eds. Harris et al., CRC: Boca Raton, Fla.), Salfeld et al. (US Patent No. 6,258,562), den Broeder et al. (Rheumatology (Oxford). 2002 Jun;41(6):638-42) and Joachim Kempeni (Ann Rheum Dis. 1999 Nov;58 Suppl 1:I70-2).

Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons:

Claims 17, 41, 79, 86, 103, 110, 115, 122, 127 and 134 of USSN 11/233,252 are directed to a method of treating rheumatoid arthritis by administering an anti-TNFα antibody, alone or in combination with additional therapeutic agents. The reference specification clarifies that the claimed methods employ antibody D2E7, i.e. the same antibody as recited in the instant claims.

Since treatment of the same disorder is claimed in copending application USSN 11/233,252 as in the instant application, i.e., rheumatoid arthritis, the symptoms of the disorder are inherently the same, and therefore are not patentably distinct from the instant claimed invention.

The instant claims differ from the reference teachings in the recitation of a "dose of 0.01 – 0.1 mg/kg."

However, as put forth in detail in Section 4 above, the reference claims, in view of the teachings of Stephens, Salfeld, den Broeder and Joachim Kempeni, render the claimed invention obvious.

Applicant argues the instant claims are non-obvious over the reference claims and cited references for the same reasons put forth by applicant in Section 4 above.

Applicant's argument are not found convincing for the reasons put forth in Section 4 above.

Thus, the reference claims, in view of the teachings of Stephens, Salfeld, den Broeder and Joachim Kempeni, render the claimed invention obvious.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 15-17, 21, 22, 24, 31, 34, 35, 42, 43, 45 and 48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating arthritis with 0.1 mg/kg of a fully human anti-TNFα antibody having the physical properties recited in claim 1, wherein the arthritis is treated as demonstrated by mean arthritic score, or for a method of treating arthritis with 0.1 mg/kg of a fully human anti-TNFα antibody having the physical properties recited in claim 1, wherein said arthritis is treated by alleviating at least one symptom selected from the group consisting of bone erosion, cartilage erosion, inflammation and vascularity, ***does not reasonably provide enablement for*** treating arthritis with 0.01-0.1 mg/kg of a fully human anti-TNFα antibody having the physical properties recited in claim 1, wherein the arthritis is treated as demonstrated by mean arthritic score, or for a method of treating arthritis with 0.01-0.1 mg/kg of a fully human anti-TNFα antibody having the physical properties recited in claim 1, wherein said arthritis is treated by

alleviating at least one symptom selected from the group consisting of bone erosion, cartilage erosion, inflammation and vascularity or for methods of treatment employing the "D2E7" anti-TNFα antibody.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

With respect to claims 34, 35 and 45, it is apparent that to practice the claimed invention the "D2E7" antibody is required. As a required element it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so available or obtainable, a deposit of the cell line(s) which produces the claimed antibody(ies) may satisfy the enablement requirement of 35 USC 112, 1st paragraph. See 37 CFR 1.801-1.809 as well as MPEP § 2400.

In the instant case, the specification generally points to U.S. Patent Nos.6,090,382 and 6,258,562 and U.S. Patent Application Nos. 09/540,018 and 09/801,185 for disclosure of "the antibody portions of the invention..." (see instant specification at page 6, last paragraph). However, while U.S. Patent Nos.6,090,382 and 6,258,562 and U.S. Patent Application Nos. 09/540,018 and 09/801,185 disclose the sequence of the heavy and light chain variable regions of the "D2E7" antibody they do not appear to disclose the sequence of the particular heavy chain constant regions found in the "D2E7" antibody. Without the sequence of the complete antibody or a cell line encoding the antibody the skilled artisan cannot practice the claimed invention because both the human light chain kappa and the IgG1 constant regions of antibodies have multiple allelic differences giving rise to constant regions of different antibody sequences (see, e.g., Atherton et al., Eur J Immunol. 2000 Sep;30(9):2540-7, in particular Table 1 and Kurth et al., Am J Hum Genet. 1991 Mar;48(3):613-20, in particular Figure 2 and Table 2).

If applicant chooses to deposit a cell line producing the D2E7 antibody under the terms of the Budapest Treaty, an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the cell line(s) which produces the claimed antibody(ies) has been deposited under the Budapest Treaty and that the hybridoma *will be irrevocably and without restriction or condition released to the public upon the issuance of a patent* would satisfy the deposit requirement made herein. See 37 CFR 1.808.

With respect to the grounds of rejection under 35 U.S.C. 112, first paragraph put forth in the prior Office Actions, applicant continues to argue the claims are enabled pointing to the data of Figures 1 and 4, emphasizing, "...Figures 1 and 4, for example, indicate that there is a dose dependent decrease in mean arthritic score compared to control mice, for example, after treatment with a 0.01 mg/kg dose and a 0.1 mg/kg dose of fully human anti-TNF antibody D2E7." (see Applicant's remarks filed December 10, 2008, paragraph bridging pages 6-7, applicant's emphasis shown).

Applicant's arguments have been considered, but have not been found convincing, essentially for the reasons of record as put forth in the Office Actions mailed August 8, 2008 and March 4, 2008.

Figures 1 and 4 display the effects of the fully human anti-TNFα antibody D2E7 on mean arthritic scores but not on, for example, bone or cartilage erosion so the data disclosed in these Figures does not address these limitations.

Moreover, neither the bone or cartilage erosion limitations, nor the mean arthritic score limitation, per se, are enabled for the scope of the claimed invention, essentially for the reasons of record as put forth in the previous Office Action actions.

In brief, MPEP § 2164.08 teaches that "[t]he focus of the examination inquiry is whether everything within the scope of the claim is enabled."

However, applicant has not established that the skilled artisan could use a dose of as little as 0.01 mg/kg to treat rheumatoid arthritis given the data disclosed in the instant specification which demonstrates no consistent effect of 0.01 mg/kg D2E7 on mice transgenic for TNFα (tg197 mice), which is one model system for rheumatoid arthritis (see, in particular, Example 1, part B and Figures 1 and 4).

As put forth in the previous Office Actions, particularly at page 5 of the Office Action mailed March 4, 2008, while the mean arthritic score of mice treated with 0.01 mg/kg of the fully human anti-TNFα antibody in Figure 4 is less than in control mice, the error bars for this data point are so large that, in comparison to the mean and error bars for control mice, the slightly decreased mean arthritic score value when measured at week 10 for Tg197 mice treated with 0.01 mg/kg D2E7 lacks statistical significance.

Furthermore, the examiner submits that Figure 4 displays the mean arthritic score as measured ***at week 10 after 10 consecutive weeks of treatment*** with the D2E7 antibody.

In contrast, Figure 1 displays the mean arthritic scores as measured at ***all weeks, i.e., weeks 1, 2, 3, 4…and at week 10*** for the D2E7 antibody. As shown in Figure 1, there were several weeks where the ***group of mice*** treated with D2E7 at 0.01 mg/kg had ***greater mean arthritic scores*** than the control group.

Thus, assuming for the sake of argument that the data applicant points to in Figure 4 were of actual statistical and practical significance, which has not yet been demonstrated, this would still not demonstrate a reasonable correlation between the scope of the claims and scope of enablement set forth because it represents the cumulative effect of 10 consecutive treatments and yet the claims are of far broader scope.

In conclusion, the examiner submits that undue experimentation would be required of the skilled artisan to practice the claimed method to the extent of its breadth in any practical sense, i.e., not only in one particular murine model for rheumatoid arthritis based on highly inbred syngeneic (clonotypic) hTNFα transgenic mice, which presumably present with a homogenous, predictable phenotype, but also in the highly outbred human rheumatoid arthritis patient population which present with a variety of clinical phenotypes and exhibit a range of sensitivity/resistance to TNFα inhibition.

Moreover, regarding in vivo methods which rely on generally unpredictable mechanisms, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling (MPEP 2164.03)." The MPEP also states that physiological activity can be considered inherently unpredictable.

In Rasmusson v. SmithKline Beecham Corp., 75 USPQ2d 1297-1303 (CAFC 2005), the court states "[W]here there is "no indication that one skilled in [the] art would accept without question statements [as to the effects of the claimed drug products] and no evidence has been presented to demonstrate that the claimed products do have those effects," an applicant has failed to demonstrate sufficient utility and therefore cannot establish enablement" and "If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to "inventions" consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the "inventor" would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis."

In conclusion, the instant claims encompass an invention of tremendous breadth, and essentially call for trial and error by the skilled artisan to begin discovering how to make and use the claimed invention without assisting the skilled artisan in such an endeavor, which is insufficient to constitute adequate enablement.

The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

Undue experimentation would be required to produce the invention commensurate with the breadth of the claims based on the disclosure of the instant specification and the knowledge

in the art. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 54 and 55 are rejected under 35 U.S.C. 102(b) as being anticipated by Le et al. (U.S. 6,277,969).

Le teaches a method for treating arthritis comprising administering to a subject the anti-TNFα antibody infliximab at a dose of 0.5 or 1.0 mg/kg, for example, once per week (see column 36, 1st and 2nd paragraphs). Le exemplifies the treatment of human arthritis patients with 1.0 mg/kg showing a decrease in arthritis symptoms in these patients, such as decreased swollen joint counts (see columns 80-89, including Table 16).

Thus, Le anticipates the instant claims.

13. Claims 54 and 55 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 54 and 55 recite a method of treatment comprising administering an anti-TNFα drug "selected from the group consisting of…enantercept."

However, the word "enantercept" does not appear in the instant specification.

Thus instant claim recites a limitation not clearly disclosed in the specification as-filed, and changes the scope of the instant disclosure as-filed. Such a limitation recited in the instant claim, which did not appear in the specification as filed, introduces a new concept and violates the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is required to cancel the new matter in the response to this Office action.

Alternatively, applicant is invited to provide sufficient written support for the limitation

indicated above. See MPEP 714.02 and 2163.06.

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ZACHARY SKELDING whose telephone number is (571)272-9033. The examiner can normally be reached on Monday - Friday 8:00 a.m. - 5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Zachary Skelding/
Examiner, Art Unit 1644
March 16, 2009